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No longer any role for Routine Follow Up Chest X-Rays in men with Stage 1 Germ Cell Cancer

De La Pena H[1†]; Sharma A[4†]; Glicksman C[4]; Joseph J[1]; Subesinghe M[2]; Traill Z[2]; Verrill C[3]; Sullivan M[7]; Redgwell J[1]; Bataillard E[4]; Pintus E[5], Dallas N[5], Gogbashian A[6]; Tuthill M[1]; Protheroe A[1§]; Hall M[4§**]

[†]These authors contributed equally to this work.

[§]These authors share last authorship.

1) Department of Oncology, Oxford University Hospitals NHS Foundation Trust.

2) Department of Radiology, Oxford University Hospitals NHS Foundation Trust.

3) Department of Pathology, Oxford University Hospitals NHS Foundation Trust.

4) Department of Medical Oncology, Mount Vernon Cancer Centre, Northwood, HA6 2RN.

5) Department of Oncology, Royal Berkshire NHS Foundation Trust.

6) Department of Radiology, Mount Vernon Cancer Centre, Paul Strickland Scanner Centre, Northwood, HA6 2RN.

7) Department of Urology and Surgery, Oxford University Hospitals NHS Foundation Trust.

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**** Corresponding author:**

Dr Marcia Hall
Department of Medical Oncology,
Mount Vernon Cancer Centre,
Northwood,
HA6 2RN, UK
Email- marica.hall@nhs.net

Abstract

Following radical orchidectomy for testicular cancer, most patients undergo protocolled surveillance to detect tumour recurrences rather than receive adjuvant chemotherapy. Current UK national and most international guidelines recommend that patients require a chest x-ray (CXR) and serum tumour markers at each follow up visit as well as regular CT scans, there is however, variation among cancer centres with follow up protocols. Seminomas often do not cause tumour marker elevation; therefore CT scans are the main diagnostic tool for detecting relapse. For non-seminomatous tumours, serum beta-HCG (HCG) and AFP levels are a very sensitive harbinger of relapse, but this only occurs in 50% of patients (1)and therefore imaging remains as important. CXRs are meant to aid in the detection of lung recurrences and prior to the introduction of modern cross sectional imaging in the early 1980s, CXRs would have been the only method of identifying lung metastasis. We examined the Thames Valley and Mount Vernon Cancer Centre databases to evaluate the role of CXRs in the 21st century for the follow up of men with stage 1 testicular cancer between 2003 and 2015 to assess its value in diagnosing relapsed germ cell tumours. From a total of 1,447 patients we identified 159 relapses. All relapses were detected either by rising tumour markers or planned follow up CT scans. Not a single relapse was identified on CXR. We conclude that with timely and appropriate modern cross-sectional imaging and tumour marker assays, the CXR no longer has any value in the routine surveillance of stage 1 testicular cancer and should be removed from follow up guidelines and clinical practice. Omitting routine CXR from follow up schedules will reduce anxiety to

patients with every visit, the time patients spend at hospitals and result in significant cost savings.

Introduction

Testicular cancer is the most common solid organ malignancy in the 15-35 year old group and one of the most curable malignancies among all cancers worldwide. Cure rates in stage 1 disease are approximately 99% and can exceed 90% in patients with metastatic disease(2, 3). The relapse rates for patients with seminoma vary depending on known risk factors such as tumour size >4cm and rete testis invasion(4) whereas for non-seminomatous or mixed tumours, lymphovascular invasion is a risk factor for recurrence(5). Despite such risk factors, approximately 83% of stage 1 seminomas and 70% of stage 1 non-seminomas will be cured with orchidectomy alone(6) and in case of relapse, >99% patients can be routinely cured with platinum based chemotherapy such as BEP (Bleomycin, Etoposide, Cisplatin / Carboplatin)(7, 8).

Although adjuvant chemotherapy has a role in reducing the relapse rates in both seminoma and non-seminomatous tumours(9), it is not routinely offered although both the SWENOTECA group and the recent BEP 111 data (using 1 cycle of adjuvant BEP in high risk non-seminomatous stage 1 patients) will become practice changing for a lot of clinicians (10, 11). In addition, given that less than 30% patients require systemic chemotherapy, it would result in gross overtreatment of over 70% of patients and exposure to the well recognised toxicities chemotherapy can cause in the short and long term such as permanent skin changes, pulmonary disease, cardiovascular disease, gastro-intestinal, renal and neurological disorders(12, 13); Close follow up to detect early relapse is therefore paramount. It has been well established that surveillance schedules are both safe and effective in identifying those who relapse and require curative chemotherapy.

The majority of relapses (>90%) occur within 2 or 3 years post orchidectomy(1) and follow up is therefore more intensive during this period, but late relapses after 5 years can also occur. Over 80% of relapses in patients with seminoma and 70% of relapses in non-seminomatous patients occur outside the chest and the most common site of recurrence are nodal masses in the retroperitoneum making chest imaging as part of routine follow up questionable(1, 9).

Follow up guidelines and imaging modalities after orchidectomy vary among centres (Table 1). Our follow up practice is based on national and international guidance such as the European Association of Urology (EAU)(14) and the National Comprehensive Cancer Network (NCCN)(15) using CXRs and CT scans routinely as shown in Table 1. Table 2 details the specific active surveillance strategies for seminoma and non-seminomatous tumours in both Thames Valley and Mount Vernon. The main differences are, that in Thames valley, a CT is performed for patients with non-seminomatous tumours at 3 years and for high-risk seminoma patients at Mount Vernon follow up is continued annually for 5-10 years.

The Thames Valley follow up for non-seminomatous tumours includes tumour markers (AFP, HCG, LDH) and CXR (except if having CT) at every clinic visit, detailed in Table 2. CT scans (Thorax abdomen and pelvis) are performed at 3 months; 1 year and 3 years post orchidectomy. At Mount Vernon the follow-up for this group is identical with the omission of LDH measurements and no CT scan at 3 years (only baseline, 3 months and 1 year; not including chest). Patients with seminoma are seen in clinic at month 1, then 3 monthly for 2 years, then 6 monthly to 5 years when those at low risk are discharged. At Mount Vernon, those with seminoma and high-risk features continue to be seen annually for a further 4-5

years. Patients with non-seminomatous germ cell tumours are seen monthly for the 1st year, then 2-monthly the 2nd year, 4-monthly the 3rd year and 6-monthly afterwards until year 5 when they are discharged.

Given the different approaches among centres regarding the utility and frequency of different imaging modalities (abdominal ultrasound, CXR, CT, MRI) in the role of testicular cancer follow up, we conducted a review of practices in the Thames Valley and Mount Vernon Cancer Centre to determine if CXRs in particular have a place in testicular cancer follow up. We identified all patients with germ cell relapse between 2003 and 2015 from the Thames Valley and Mount Vernon databases who relapsed having presented with Stage 1 disease. We identified the number of CXRs performed for each patient as part of their surveillance and reviewed the images or reports. We assessed the incidence and location of relapse, as well as the methods by which these relapses were detected.

Methods

The Thames Valley database was designed using MySQL relational database management system in a Trust Server; a web based front-end application with secured login and password to maintain patient confidentiality. All new cases are discussed at multi-disciplinary team (MDT) meetings where pathology and radiology are centrally reviewed and appended to the database by an automated process and updated regularly with clinical follow up data. This publication is a retrospective assessment of a combination of all Stage I germ cell cases offered surveillance at diagnosis and registered at Mount Vernon Cancer Centre (Northwick Park, North Middlesex, Watford, Luton & Dunstable, Stevenage, Hillingdon) and Thames Valley (Oxfordshire, Milton Keynes, Reading, High Wycombe, Stoke Mandeville, Swindon and Slough) between 2003 and 2015. Ethical approval was not required for this service evaluation audit, which is registered in the UK's National Clinical Audits directorate (ID number: 4072) via the Oxford University Hospitals, NHS Foundation Trust and East and North Hertfordshire NHS Trust (ID number: 10215).

Results

We identified 1,447 patients with a confirmed diagnosis of testicular cancer (886 seminomas, 561 non-seminomas) who underwent orchidectomy between 2003 and 2015. 11 patients with seminoma and 14 patients with non-seminomatous tumours were lost to follow up due to transfer of care to other centres. There were 164 confirmed relapses. Five relapsed patients from Thames Valley were excluded from the analysis due to lack of information (no clinical notes or electronic information available) leaving a total of 159 patients with relapsed testicular cancer (Table 3).

For patients with seminoma, 89% (n=74) of all relapses occurred within the abdomen (Table 4), 4% (n=3) in the mediastinum and 1% (n=1) in the lung. 1 patient developed a contralateral second primary germ cell tumour. Relapse was identified in 6% (n=5) based on raised tumour markers alone with no measurable disease (biochemical relapse). The patients who developed lung metastases did not have abnormal CXR findings, despite a contemporaneous CT scan confirming relapse. 84% (n=70) of relapsed seminomas were detected on routine CT scans, 15% (n=12) through raised tumour markers, prompting early CT scan and 1% (n=1) on abdominal MRI. No relapse was detected on CXR (Table 6).

For patients with non-seminomatous tumours, 85% (n=64) of relapses occurred in the retroperitoneum, 4% (n=3) in the mediastinum, 5% (n=4) in the lungs, 1% (n=1) in brain/spine and in 5% (n=4) treatment for relapse was based on raised tumour markers alone (Table 4). 62% (n=47) of non-seminoma relapsed patients were identified initially on CT scan and 38% (n=29) by raised tumour markers (Table 5). Of those patients with lung metastases (5%, n=4), only one patient had CXR

changes, however this patient's AFP had risen to 4,000, which triggered an early CT scan confirming lung metastases; the CXR was unnecessary. Lung metastases were not seen on CXRs performed concurrently with routine surveillance CTs in 4 patients.

Incidental findings were detected on surveillance CXR in this population: one case of tuberculosis, one lobar pneumonia and one small pneumothorax were identified in the Mount Vernon population over this period. The mean time to relapse in the lungs post orchidectomy for seminomas was 11.5 months (from 4 to 19 months) and for non-seminomas was 6.3 months (from 2 to 13 months). Over half of patient with lung metastasis had concomitant retroperitoneal nodal relapse.

Discussion

The frequency and schedule of surveillance CXRs, CTs (or MRIs) used in testicular cancer follow up varies between countries and centres. Most centres use a total of 3 to 5 CT scans over a 5-year period. Some centres, such as Mount Vernon, only image (CT) the retroperitoneum / abdomen (excluding chest) to minimise radiation exposure where appropriate(5, 6, 14, 15).

CTs have a much better predictive value compared to plain CXR in detecting lung metastases(16). Both these imaging modalities involve exposure to ionising radiation, which should be minimised due to an increased risk of secondary malignancies, particularly in this young patient population expected to live a normal life expectancy after successful treatment. The CXR played a pivotal role in the diagnosis of chest pathology before the mid 1980's, prior to the widespread availability of CT imaging(17). It is likely that many germ cell surveillance protocols only include CXR now, as it was firmly embedded in routine clinical practice from this time. Worldwide, guidelines do not always keep up with the speed of technological advances. As novel imaging modalities are introduced and shown to be safe and more effective, they should be introduced to replace older modalities. Studies have been exploring the optimal frequency and mode of cross sectional imaging for retroperitoneal relapse. The TRISST(18) trial is aiming to address the frequency of surveillance CTs and MRIs for patients with stage 1 seminoma (results awaited). The TE08 study(19) described the non-inferiority of undertaking 2 versus 5 additional CT scans (after initial staging) for the reassessment of patients with stage 1 non-seminomatous germ cell tumours. No prospective study has evaluated the ongoing role for CXR. This is particularly important because it is likely that

with the improved ability to detect nodal relapse, fewer patients will go on to develop visceral metastases (i.e. lung) nowadays, as they are likely to be treated earlier.

According to the Thames Valley / Mount Vernon guidelines, a patient with a seminoma will require 12 CXRs and those with non-seminoma 22 CXRs during 5 years of follow up. Similarly in Australia, the reported average number of CXR is 9 for patients with seminoma and 10 for patients with non-seminoma undergoing surveillance(20). The range of CXR's was 0-30, which is similar to this review. It is difficult to accurately calculate the expense and cost per CXR during the 12-year period analysed in this study. It is also debatable whether the cost per CXR should include the cost involved in reporting by radiologists. Therefore the cost of a single CXR can vary from £26 to £100. Every network/Trust will therefore spend from £312 to £1,200 per seminoma patient on CXRs alone and £572 to £2,200 per non-seminomatous patient. To date, it is estimated that Mount Vernon Cancer Centre and the Thames Valley germ cell surveillance practice has cost between £607,880 to £2,338,000 in CXRs alone for the low (£26) and high (£100) estimates of CXR quotes.

Repeated CXRs increase the radiation exposure to these, often young, adults. The dose of a typical postero-anterior CXR is 0.014mSv, which corresponds to a lifetime risk of detriment from fatal cancer of approximately 1 in 1 million(21-23). This compares with the natural lifetime risk of fatal cancer of approximately 1 in 3. It is equivalent to the risks from natural background radiation of 3 days. The radiation exposure per CXR is very low and should not be significant in isolation, however

repeated unnecessary exposure should be avoided. If a patient completes all planned CXRs on their surveillance program, they will receive 0.168mSv and 0.308mSv as a cumulative dose per seminoma and non-seminomatous diagnosis, (36 and 66 days of natural background radiation) respectively.

We have described the use of CXR in the routine surveillance of a large cohort (1,447) of germ cell cancer patients. Other centres and series have shown similar results (Table 6). Cunniffe et al examined their relapse rate in over 6,000 patients with stage 1 seminomas and non-seminomas over a 10-year period (2000–2010)(24). As part of this analysis it was apparent that no relapse was identified from CXR. Kolmannsberger et al investigated 221 relapses out of 2,483 stage 1 seminoma and non-seminomatous tumours over a 12-year period (1998-2010)(1). Two patients (0.08%) had their recurrent germ cell tumour diagnosed from routine CXRs. Daugaard et al analysed 382 relapses in their 1,226 patient population (1984-2007 period) with stage 1 non seminomatous tumours including high risk patients with lymphovascular invasion, rete invasion and embryonal carcinoma components; once again tumour markers detected early relapse and CTs late relapse with CXRs playing no role(25). Cummins et al showed 1 patient had germ cell tumour recurrence detected by CXR from 22 relapses in their 164 stage 1 seminoma cohort(26). Following a review by Tolan et al., where 527 patients with stage 1 seminoma were investigated and 73 of 74 relapses were detected by CT abdomen-pelvis, none on CXR alone, Canadian clinicians (as the SWENOTECA group) reviewed their national guidance and have omitted routine CXR from their surveillance protocols(26, 27).

With modern CT scanners and reliable tumour markers, we conclude that from our review, CXRs no longer have a role in diagnosing germ cell tumour relapse. 89% of seminomas metastasise outside the chest and CXR did not detect any of the proven lung metastases identified by CT scanning. 85% of non-seminomas relapse outside the chest. A single case of lung relapse was detected by CXR after AFP of 4,000 triggered imaging (CT scanning). In this study, lung relapses (detected by CT) were not evident on concurrent CXRs. Additionally, misleading CXRs with nipple shadows or other artefacts, can lead to extra unnecessary CT scans (data not shown) and anxiety for patients.

As in Canada and the SWENOTECA group, we suggest that other centres both nationally and internationally should change their clinical practice and current guidelines should be reviewed in line with these findings. We hope these core data become an integral and fundamental pillar in forming uniform national germ cell surveillance follow up guidelines. Similarly, we also show here that clinical examination has limited value in diagnosing germ cell relapse, supporting the rationale for patients to undergo a less onerous follow up protocol regime based on tumour markers and CT scans alone, as poor patient compliance (data not shown) in the follow up schedule can be an issue in this young patient population.

Following surgery, strategies to maintain safe and adequate surveillance with measurement of tumour markers and limited cross-sectional imaging are required. Some of this population need reminding of the importance of complying with these interventions. Reducing the number of mandatory hospital visits may help in this respect. Revision of national UK surveillance guidelines to exclude routine CXR

is a first step and perhaps the use of more modern technology such as smart phone applications, which are increasingly being used in the medical field, will drive further modifications to improve patient compliance with surveillance programmes.

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TABLE 1: International protocols for Surveillance follow up in Stage 1 germ cell tumours

Group	Year of follow up	Clinic/markers	CT A+P	CXR
ESMO	1	3m	6m	6m
	2	3m	6m	6m
	3	4m	Annually	Annually
	4	6m	Annually	Annually
	5	6m	Annually	Annually
	6-10	Annually		
SIGN	1	3m	6m	3m
	2	3m	6m	3m
	3	6m	Annual	6m
	4	6m	Annual	6m
	5	6m	-	6m
	6-10	Annually	-	Annually
NCCN	1	2m	4-6m	Twice
	2	3m	6-12m	Annually
	3	4-6m	Annually	Annually
	4	6m	12-24m	Annually*
	5	Annually	12-24m	Annually*
EAU- Seminoma	1	4m	6m	6m
	2	4m	6m	6m
	3	Annually		Annually
	4	Annually		
	5	Annually		Annually
EAU- NSGCT	1	3m	3 &12m	6m
	2	3m	Annually	6m
	3	3m	Annually	6m
	4	Annually		6m
	5	Annually		6m

ESMO: European Society Of Medical Oncology; SIGN: Scottish Intercollegiate Guidelines Network
*Seminoma- Only if clinically indicated- CT chest in symptomatic patients
m= months
EAU- European Association of Urology

Table 2: Follow up schedule at MVCC and Thames valley

ORGANIZATION	Year of follow up	Clinic/markers	CT A+P	CXR
Thames Valley-Seminoma	1	1m then 3m	3 & 12m*	1m then 3m
	2	3m		3m
	3	4m	Annually*	4m
	4	6m		6m
	5	6m		6m
Thames Valley-NSGCT	1	Monthly	3 & 12m*	Monthly
	2	2m		2m
	3	4m	Annually*	4m
	4	6m		6m
	5	6m		6m
MVCC	1	3m	6m, 12m	3m
	2	3m	24m,	3m
	3	4m	36m	4m
	4	6m		6m
	5	6m Discharge if low risk		6m
	6-10	12m		Alt 12m
*Thames valley had CT Thorax as well as part of Surveillance follow up				

TABLE 3: Patients demographics

Centre	Number of evaluable relapses (range)	
MVCC	100	
Thames Valley	59	
Total	159$^{\Psi}$	
Median age at diagnosis	34 years (11-86)	
Median number of CXR**	12 (0-34)	
Stage at Presentation	Seminoma	Non-seminomas
Stage 1	89% (n=83)	81% (n=76)
TOTAL= 159	n=83	n=76
$^{\Psi}$ excluded due to insufficient data		
* Thames Valley cohort only		
**MVCC		

TABLE 4: Nature of relapse

Site of Relapse	Seminomas	Non-Seminomas
Abdo/Pelvis*	89% (n=74)	85% (n=64)
Mediastinum	4% (n=3)	4% (n=3)
Lungs	1% (n=1)	5% (n=4)
Brain/Spine	0% (n=0)	1% (n=1)
Biochemical Relapse**	6% (n=5)	5% (n=4)
Total	100% (n=83)	100% (n=76)

NOTE: *Abdomen/Pelvis: Includes Iliac, retroperitoneal, retro-precaval, paraaortic and liver metastasis. **Biochemical Relapse: Positive tumour markers without objective anatomical relapse on imaging.

Table 5: Modality of relapse detection

Relapse Detection	Seminomas	Non-Seminomas
CT Scan	84% (n=70)	62% (n=47)
Tumour Markers	15% (n=12)	38% (n=29)
CXR	0% (n=0)	0% (n=0)
MRI	1% (n=1)	0% (n=0)
Total	100% (n=83)	100% (n=76)

TABLE 6: Published Multicentre Analyses which detail role of CXR

Author, publication year (actual years and type GCT reviewed)	Germ Cell Cases on Surveillance	Relapses Diagnosed By CXR
De La Pena et al, 2017 (2003-2015, seminoma and non-seminoma)	1447	0
Cunniffe et al, 2012 (2000-2010, seminoma and non-seminoma)	6000	0
Kolmansberger et al, 2015 (1998-2010, seminoma and non-seminoma)	2483	2
Daugaard et al, 2014 (1984 – 2007, non-seminoma)	1226	0
Cummins et al, 2009 (1980 – 2004, seminoma)	164	1
Tolan et al, 2010 (1982 – 2005, seminoma)	527	0
Total	11847 (100%)	3 (0.02%)